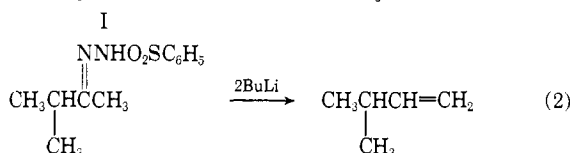
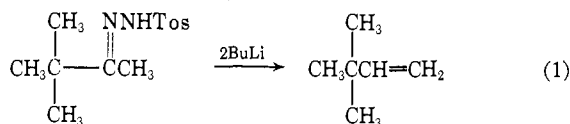


## Reactions of Butyllithium with Sulfonylhydrazones

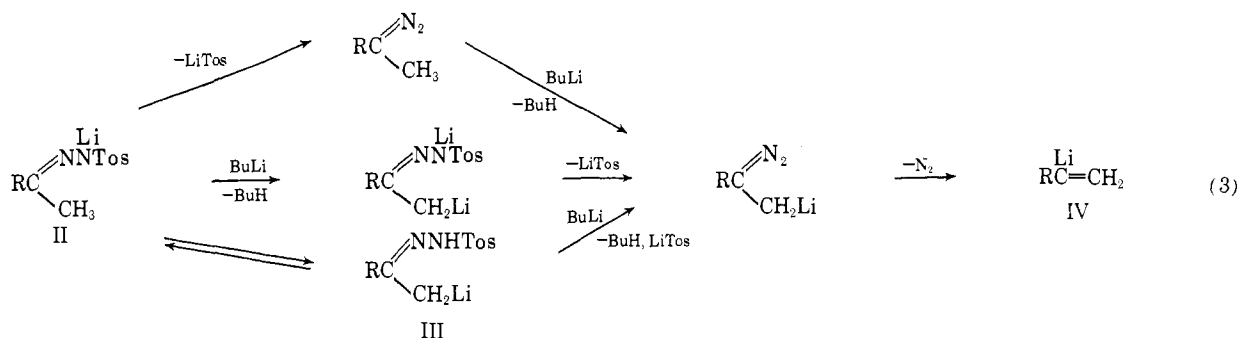
Sir:

We wish to describe advantageous new reactions and methods based on butyllithium and sulfonylhydrazones and experiments which elaborate the effects in such systems.

Sulfonylhydrazones having  $\alpha$ -hydrogens react with  $\cong 2$  equiv of butyllithium to give olefins. Thus 3,3-dimethyl-2-butanone *p*-tosylhydrazone (I) reacts heterogeneously with sufficient butyllithium at 70–90° in <1 min to give 3,3-dimethyl-1-butene quantitatively (eq 1).<sup>1</sup> Benzenesulfonylhydrazones of 3-methyl-2-



butanone (eq 2) and of 2-pentanone yield 3-methyl-1-butene and 1-pentene, respectively. With proper stoichiometry butyllithium (2 equiv) thus effects decomposition of sulfonylhydrazones without carbon







skeleton rearrangement or insertion to cyclopropanes and leads to lesser substituted olefins.<sup>2</sup>

The effects of stoichiometry of butyllithium on decomposition of I are summarized in Table I. Reaction of I with <1 equiv of butyllithium results in competitive cationic and carbenic processes to give mixtures of 3,3-dimethyl-1-butene, 1,1,2-trimethylcyclopropane, 2,3-dimethyl-1-butene, and 2,3-dimethyl-2-butene. With 1 equiv of butyllithium, reaction occurs carbenically almost completely to yield 3,3-dimethyl-1-butene (57%) and 1,1,2-trimethylcyclopropane (40%). Increased amounts (1.2–1.8 equiv) of butyllithium in decalin increase production of 3,3-dimethyl-1-butene with corresponding exclusion of 1,1,2-trimethylcyclopropane. A similar effect occurs in diethyl Carbitol; however, more butyllithium is required because of its destruction by the solvent. Butyllithium in decalin or in diethyl Carbitol at temperatures up to 150° does not isomerize

(1) We became aware of similar work by R. H. Shapiro and M. J. Heath *via* Abstracts of Papers of the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. On learning of our efforts, Dr. Shapiro volunteered to delay publication of their observations until our manuscript had been submitted. We acknowledge the friendly exchange with Dr. Shapiro.

(2) Additional examples of the effects of excess butyllithium on tosylhydrazones have been separately submitted for publication by J. H. Robson and H. Shechter.

Table I. Effects of Butyllithium on Decomposition of 3,3-Dimethyl-2-butanone Tosylhydrazone

Base	Equiv	Solvent	Products, %			
						
BuLi <sup>a</sup>	0.5	Decalin	36	11	38	18
	0.8		41	18	28	13
	1.0		57	40	3	
	1.2		81	19		
	1.4		95	5		
	1.6		98	2		
	1.8		100			
	2.0		100			

<sup>a</sup> The reagents were mixed, pentane was removed, decalin was added, and the mixture was heated rapidly to 70–110°.

1,1,2-trimethylcyclopropane to olefins. The over-all effects of butyllithium on sulfonylhydrazones are similar to that of excess (7–8 equiv) sodium amide at much higher temperatures.<sup>3</sup>

The action of excess strong base on a lithium salt of a sulfonylhydrazone (II) is of interest in that there is eventual attack on  $\alpha$ -hydrogen as controlled by steric and/or electrical factors, possibly *via* the carbanionic sequence indicated (eq 3), to give the lithio olefin IV and thence the olefin by exchange with the environment.<sup>4</sup>

The susceptibility of tosylhydrazone anions to base and the possible relationship to eq 3 have compelled investigation of deuterium exchange into tosylhydrazone salts in ethylene glycol-*d*<sub>2</sub> and in tetrahydrofuran-*D*<sub>2</sub>O. From the deuterium content of the recovered tosylhydrazones (Table II), there is indeed rapid exchange into  $\alpha$  positions as predicted by interconversion of II to III and transfer with the deuterium donor. The much greater rate of incorporation of deuterium into lithium cyclohexanone tosylhydrazone than for lithium cyclopentanone tosylhydrazone<sup>5</sup> along with the resistance of the diisopropyl ketone tosylhydrazone system to exchange allow the preliminary conclusion that there is a strong steric effect in formation of anions such as III. Further information relative to the mechanism sequence is that  $\alpha$ -thioethoxyacetophenone *p*-tosylhydrazone is converted by >2 equiv of butyllithium in tetrahydrofuran to its dilithio salt V.<sup>2,6</sup> No matter

(3) W. Kirmse, B. G. von Bulow, and H. Schepp, *Ann.*, **691**, 41 (1966).

(4) The present carbanion mechanisms differ in part from that of ref 3 and of M. Fischer, Z. Pelah, D. H. Williams, and C. Djerassi, *Ber.*, **98**, 3236 (1965).

(5) (a) For a discussion of *exo* and *endo* unsaturative effects in five- and six-membered ring systems see H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

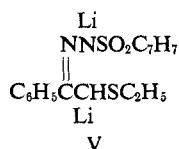
(6) Deuterium exchange of sulfonylhydrazone anions in ethylene

**Table II.** Deuterium Exchange of Lithium Salts of Tosylhydrazones in Ethylene Glycol- $d_2$  and in Tetrahydrofuran- $D_2O$

Tosylhydrazone of	Temp, °C	Time, hr	Number (percentage) of deuterium atoms incorporated
Acetone <sup>a</sup>	71	6.3	0 (5), 1 (17), 2 (31), 3 (30), 4 (17), 5 (<1)
Cyclopentanone <sup>a</sup>	71	6.3	0 (32), 1 (37), 2 (22), 3 (8), 4 (1)
Cyclohexanone <sup>a</sup>	71	6.3	0 (5), 1 (17), 2 (13), 3 (30), 4 (17), 5 (<1)
Diisopropyl <sup>b</sup> ketone	30	115	0 (94), 1 (6), 2 (<1)

<sup>a</sup> Pure lithium salt (0.01 mole) was heated with ethylene glycol- $d_2$  (0.09 mole, >99%  $d_2$ ); the tosylhydrazone was regenerated with equivalent amounts of  $D_2SO_4$ , converted to its lithium salt by reaction with butyllithium in ether, and pyrolyzed dry to hydrocarbons which were analyzed mass spectrometrically at low voltages. <sup>b</sup> This tosylhydrazone was exchanged in tetrahydrofuran (50 ml)—99.7%  $D_2O$  (0.30 mole).

what the details of the mechanics of reaction of excess butyllithium with sulfonylhydrazones are, what we wish to emphasize at present is that sulfonylhydrazones undergo facile deuterium exchange of their  $\alpha$ -hydrogens, and such methods in conjunction with decomposition of sulfonylhydrazones *via* cationic, carbenic, and  $\alpha$ -elimination processes should be valuable for synthesis of deuterated compounds.



Lithium and sodium salts of aldehyde *p*-tosylhydrazones decompose efficiently at reduced pressures to pure primary diazoalkanes.<sup>7</sup> Salts of *p*-tosylhydrazones of unbranched ketones decompose at higher temperatures than those of aldehydes, and the secondary diazo compounds formed do not survive (~5%) pyrolysis.<sup>7</sup> It has now been found that (1) the decomposition temperatures of lithium salts of *p*-tosylhydrazones as solids, in suspension or in solution, are considerably lower than those of sodium salts, and (2) salts of *p*-tosylhydrazones of  $\alpha$ -substituted ketones decompose at lower temperatures (30–40°) than do their unsubstituted analogs. It is now possible to convert lithium salts of *p*-tosylhydrazones of ketones such as 3-methyl-2-butanone and 3,3-dimethyl-2-butanone to 2-diazo-3-methylbutane and 2-diazo-3,3-dimethylbutane in 90–95% yields and >98% purity by vacuum pyrolysis. Highly unstable and involatile diazo compounds such as 2-diazo-1-phenylpropane and 2-diazo-1,3-diphenylpropane can now be prepared by the pyrolytic method at 80–120°. It is suggested that the lower decomposition temperatures of salts of *p*-tosylhydrazones of substituted ketones result primarily from *cis* strain release in conversion to products containing the linear diazo function.

glycol- $d_2$  is being investigated kinetically to determine if sulfonylhydrazone dianions are being generated under these conditions.

(7) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Am. Chem. Soc.*, **87**, 935 (1965).

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G. Kaufman, F. Cook, H. Shechter  
Chemistry Department, Ohio State University  
Columbus, Ohio

J. Bayless, L. Friedman  
Chemistry Department, Case-Western Reserve University  
Cleveland, Ohio  
Received September 5, 1967

### The Structure of Monensic Acid, a New Biologically Active Compound

Sir:

We wish to report the structure of a biologically active compound produced by a new strain of *Streptomyces cinnamomensis*. This compound, which has been named monensic acid,<sup>1</sup> is a potent inhibitor of alkali metal cation transport into rat liver mitochondria<sup>2</sup> and has broad-spectrum anticoccidial activity.<sup>3</sup>

Monensic acid ( $C_{38}H_{62}O_{11}$ , mol wt 670)<sup>4</sup> has mp 103–105°,  $\nu_{\text{max}}^{\text{CHCl}_3}$  3236 (OH) and 1695  $\text{cm}^{-1}$  (C=O),  $pK_a' = 6.65$  (66% DMF), and exhibits no ultraviolet absorption maximum above 210  $\mu$ . The 1695- $\text{cm}^{-1}$  band, attributed to the carboxyl group, moved to 1563  $\text{cm}^{-1}$  in the sodium salt. The nmr spectrum<sup>5</sup> indicated the presence of a single methoxyl group at  $\delta$  3.37 ppm. The acid and its alkali metal salts are only slightly soluble in water (*ca.* 0.1 mg/ml), but are soluble in most organic solvents.

Monensic acid formed a diacetate ( $C_{40}H_{66}O_{13}$ ),<sup>6</sup>  $pK_a' = 7.60$  (66% DMF),  $\nu_{\text{max}}^{\text{CHCl}_3}$  3448 (OH) and 1727  $\text{cm}^{-1}$  (C=O) with acetic anhydride-pyridine. Treatment of the diacetate with diazomethane in ether gave a crystalline methyl ester ( $C_{41}H_{68}O_{13}$ , calcd mol wt, 768; found, *m/e* 768), mp 113–114°,  $\nu_{\text{max}}^{\text{CHCl}_3}$  3546 (OH) and 1724  $\text{cm}^{-1}$  (C=O). That a primary and a secondary hydroxyl had been acetylated was inferred from the presence of an AB quartet centered at  $\delta$  4.08 ppm and a partially resolved multiplet at  $\delta$  4.72 ppm. Monensic acid reacted with 1 mole of periodate to yield formaldehyde as one of the products. The deshydroxymethyl oxidation product, obtained as an amorphous solid, upon acetylation (acetic anhydride-pyridine) and treatment with diazomethane gave a crystalline monoacetyl methyl ester ( $C_{38}H_{62}O_{11}$ , calcd mol wt, 694, found, *m/e* 694), mp 130.5–132.5°,  $\nu_{\text{max}}^{\text{CHCl}_3}$  1724  $\text{cm}^{-1}$  (C=O), partially resolved multiplet at  $\delta$  4.72 ppm.

These results suggested that monensic acid contained vicinal primary and tertiary hydroxyl groups and an isolated secondary hydroxyl group, which together with the carboxyl and methoxyl groups accounted for six of the eleven oxygen atoms. The remaining five were assumed to be present as ethers. Since no double

(1) A detailed report of the discovery and isolation of monensic acid will be published by M. E. Haney, Jr., and M. M. Hoehn.

(2) S. Estrada-O., B. Rightmire, and H. Lardy, to be published.

(3) R. F. Shumard and M. E. Callender, to be published.

(4) The molecular formula of monensic acid is derived from the high-resolution mass spectrum of its sodium salt: calcd mol wt for  $C_{38}H_{61}O_{11}Na$ , 692.41117; found, *m/e* 692.41375. Mass spectra of the free acid typically exhibit no peak for the molecular ion. The highest mass peak (*m/e* 634) corresponds to the loss of two molecules of water.

(5) The nmr spectra were recorded in  $CDCl_3$  solution with TMS as the internal reference unless indicated otherwise.

(6) Satisfactory elemental analyses were obtained for all compounds whose molecular formulas are given.